Determination of Absolute Configuration of the Alkyl Group at the a-Position in the Acyclic α-Alkyl-(E)-β,γ-Enoates by Circular Dichroism

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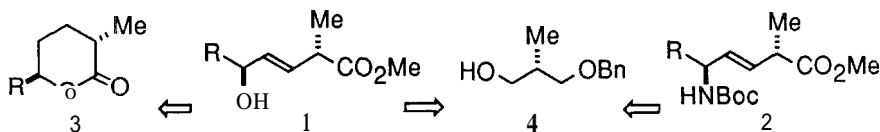
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Abstract: The absolute configuration at the a-alkylated carbon center in y-oxygenated or γ-aminated α,β-unsaturated esters can be determined by circular dichroism measurement with confidence. Whereas (2S)- compounds show a positive n $\longrightarrow \pi^*$ Cotton effect around 220 nm, (2R)-series of compounds exhibit a negative n $\longrightarrow \pi^*$ Cotton effect near 220 nm. Thus, given the sign of the n $\longrightarrow \pi^*$ Cotton effect one can determine the absolute configuration at the a-position in the a-alkyl-(E)-α,β-unsaturated ester. The presence of oxygentated or aminated group at the &position does not exert any influence on the sign of n $\longrightarrow \pi^*$ Cotton effect.
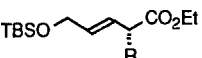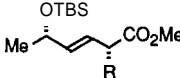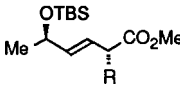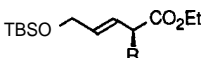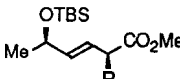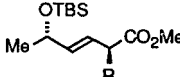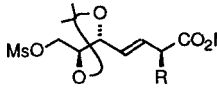
Homochiral δ-hydroxy-(E)-β,γ-enoate (**1**) is an important chiral building block for the synthesis of natural products, since both (E)-allylic alcohol and ester functions are available for further chemical manipulation.[1] In addition, isostere (**2**), possessing high lipophilicity and enhanced resistance to enzymatic hydrolysis, has attracted increasing interest in recent years.[2,3] Recently, both **1** and 2 have been synthesized in high chemical and optical yields by organocopper-Lewis acid mediated reaction of y-mesyloxy- α,β-enoates.[1,2] The assignment of the absolute configuration of the alkyl group at the a-position could be predicted by the well known anti-SN2' attack of organocopper reagents.[4] However, unequivocal stereochemical assignments were not possible on this basis alone, because some exceptions to the anti-SN2' reaction pathway have been reported.[5] The absolute configuration at the a-position of chiral y-oxygenated or aminated a-alkyl-P,y-enoates (**1**) or (2) were secured by multi-step conversion into the known compounds 3 and/or 4. [1,2] A similar chemical degradation for the determination of absolute configuration of organocopper reaction products has recently been reported.[4a,f,g]

As stated above, determination of the absolute configuration by chemical means was a rather tedious and time consuming task. These chemical methods are unacceptable if sufficient quantities of the material are not available. In conjunction with our work, a simple, fast, and reliable method for determination of the absolute configuration of a-alkyl group in homochiral a-alkyl-P,y-enoates is required.
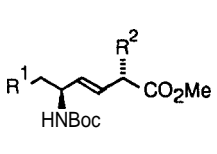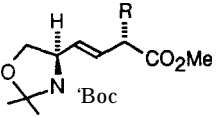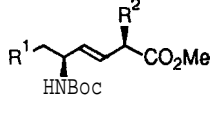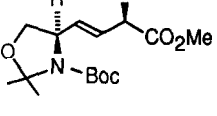
It has been well documented that most chiral β,γ-unsaturated carbonyl compounds,[6-9] including α-phenylacetic acids,[10,11] their esters,[11] and the corresponding a-phenyl ketones, exhibit unusually high CD ellipticities and ORD amplitudes.[12] The n → π* Cotton effect has been correlated with the molecular structure of β,γ-unsaturated carbonyl compounds, resulting in the formulation of the "extended or generalized" Octant rule.[8,12,13] For compounds with rigid conformations, the rule is highly reliable for the determination of absolute configuration at the a-position of β,γ-unsaturated carbonyl compounds. In flexible acyclic systems, conformational effects are highly important because the sign of the n → π* Cotton effect resulting from the homoconjugated systems might be reversed owing to conformational changes. In other words, the observed Cotton effect cannot always predict the absolute configuration at the a-position based on the empirical model of the "extended" Octant rule. In fact, the rule could not be applied to some steroidal β,γ-unsaturated esters [14] and spiro compounds.[15] Most of the few cases of anti-Octant have derived from atoms or groups lying close to the Octant rule nodal surfaces. Consequently, the organic chemists have been advised to use the extended Octant rule only with great caution.[7,16]

Table I. Circular Dichroism n → π* Cotton Effect Data
for a-Alkyl-y-oxygenateded-Q-P,y-unsaturated Esters

structure	entry	compound		A ε (nm) (in isooctane)	abs. configuration at the a-position	[a],, deg $cm^2 g^{-1}$ (in CHC13)
TBSO ⁓⁓CO₂Et / R	1	**5**	(R = Me)	- 3.27 (216)	*R*	- 21.5
	2	6	**(R = Bu)**	- 4.18 (217)	*R*	- 27.3
OTBS / Me⁓⁓CO₂Me / R	3	7	(R = Me)	- 3.42 (216)	*R*	- 31.2
	4	8	**(R = Bu)**	- 2.97 (216)	*R*	- 37.2
OTBS / Me⁓⁓CO₂Me / R	5	9	(R = Me)	- 4.65 (216)	*R*	- 30.9
	6	10	(R=Pr)	- 4.69 (216)	*R*	- 42.8
	7	**11**	(R = Bu)	- 5.33 (216)	*R*	- 37.2
TBSO ⁓⁓CO₂Et / R	8	12	(R = Me)	+ 3.27 (216)	S	+22.1
	9	13	**(R = Bu)**	+ 4.18 (217)	S	+29.7
OTBS / Me⁓⁓CO₂Me / R	10	14	**(R = Me)**	+ 3.42 (216)	S	+31.5
	11	15	**(R = Bu)**	+ 2.97 (216)	S	+ 37.4
OTBS / Me⁓⁓CO₂Me / R	12	16	**(R = Me)**	+ 4.67 **(216)**	S	+ 30.8
	13	17	(R = Pr)	+ 4.69 (216)	S	+ 42.2
	14	18	(R = Bu)	+ 5.29 (216)	S	+ 39.4
MsO⁓...O...CO₂Me / O R	15	19	(R = Me)	+ 3.88 (213)[a]	S	- 25.0
	16	20	(R = Bu)	+ 3.89 (215)[a]	S	- 6.73

[a] Methanol solvent.

Table **II.** Circular Dichroism n → π* Cotton Effect Data for Protected (*E*)-CH=CH Isosteric Dipeptides[a]

structure	entry	compound	$\Delta\varepsilon$ (nm) (in isooctane)	stereochem. at the α-position	$[\alpha]_D$ deg cm^{2}g^{-1} (in CHCl$_3$)
	1	**21** (R^1 =H, R^2 = Me)	+ 5.26 (217)	*S*	+ 2.14
	2	**22** (R^1 = OTBS, R^2 = Me)	+ 5.69 (218)	*S*	+ 33.1
	3	2 3 (R^1 = OTBS, R^2 = iso-Bu)	+ 4.41 (217)	S	+ 44.1
	4	**24** (R^1 = Ph, R^2 = Me)	+ 5.70 (222)[b]	*S*	+ 36.4
	5	25 (R^1 = Ph, R^2 = iso-Bu)	+ 6.15 (222)[b]	S	+ 49.6
			+ 6.80 (216)	S	+ 27.1
	I	26 (R = Me) 2 2 8 7 (R = iso-Bu)	+7.69 (212)	S	+ 40.3
		(R benzyl)	+ 5.00 (224)[b]	S	+ 29.8
				R	- 17.i
				R	- 39.8
	10 11 9	31 (R^1 29 (R^1 = OTBS, R^2 = Me) 30 (R^1 = = Ph, R^2 = Me) = OTBS, R^2 = = iso-Bu)	- 4.05 5.60 3.70 (216) (216) (225)[b]	R	- 18.5
	12	3 2 (R^1 Ph, R^2 iso-Bu)	- 4.24 (227)[b]	R	- 42.6
				R	- 31.6
	13 14	3 33 4 (R = Me) (R = iso-Bu)	- 3.73 4.77 (219) (218)	R	- 61.2
	15	**35** (R = benzyl)	4.33 (224)[b]	R	- 73.5

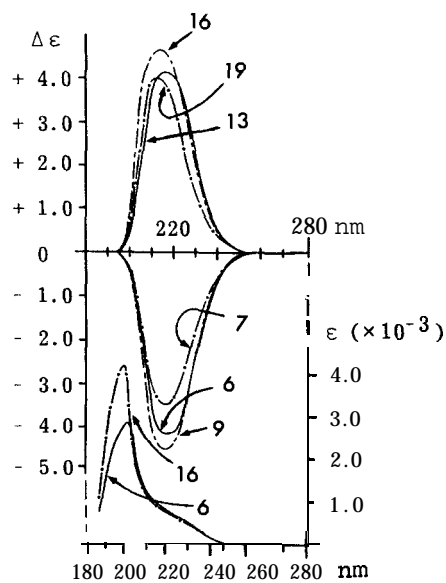[a] OTBS = rat-Butyldimethylsilyloxy. [b] Relevant ellipticity to the n → π* Cotton effect was presented.

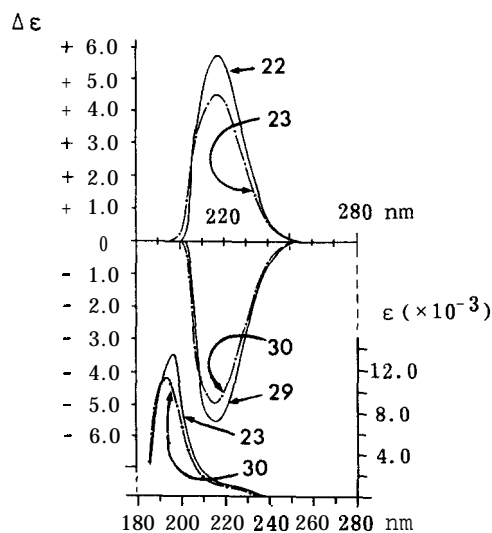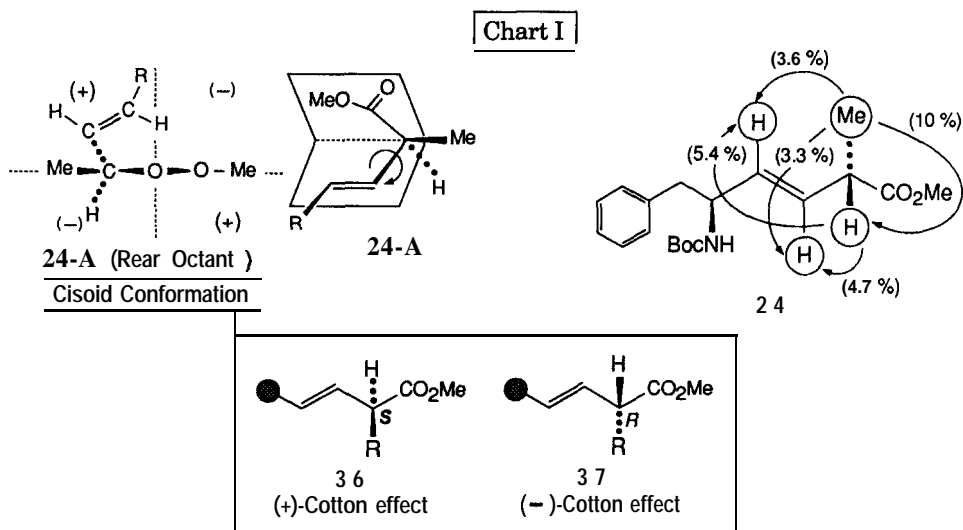Fig. 1. **CD spectra of 6,7,9,13,16, and 19** (in isooctane) and UV spectra of 6 and 19 (in isooctane).

Fig. 2. **CD spectra of 22,23,29, and 30** (in isooctaue) and UV spectra of 23 and 30 (in isooctane).

This paper describes circular dichroism study directed toward this problem. The data presented in Table **I** and II summarize the position, magnitude, and sign of the ellipticity band(s) of selected γ-oxygenated-α-alkyl-(E)-β,γ-enoates and (*E*)-alkene isosteres in solution. All of the compounds examined show a highly diagnostic CD Cotton effect at around 220 nm. The observed Cotton effect suggests that the carbonyl group adopts preferred conformations. **Figures 1** and **2 are** shown as typical examples.

It is well known that the extrema in the CD curves usually coincided with the UV maxima. However, the n ⟶ π* transitions in the UV spectra of the α-alkyl-(*E*)-β,γ-enoates were not included in Tables I and II, because they overlap and lie on the slope of the π ⟶ π* absorption as can be seen from **Figures I** and **II.**

In **Chart I,** a preferred conformation 24-A of Boc-Phe-ψ-[(*E*)-CH=CH]-D-Ala-OMe (**24**)(**Table** II, entry 4) resulting from rotation about the C(α)-C(β) bond were drawn on the basis of the NOE measurements. Thus, irradiation of the C-2-methyl hydrogens at δ 1.19 enhanced the integrated signal areas at δ 3.11 (C-2-H; ca. 10%), δ 5.49 (C-4-olefinic H; ca. 3.6 %), and δ 5.57 (C-3-olefinic H; ca. 3.3 %). In turn, irradiation of the C-2-hydrogen at δ 3.11 enhanced the intensities of the signals at δ 1.19 (C-2-methyl; ca. 8.3 %), δ 5.49 (C-4-H; ca. 5.4 %), and δ 5.57 (C-3-H; ca. 4.7 %). The present ^{1}H-NMR results with Boc-Phe-v-[(E)-CH=CH]-D-Ala-OMe may be interpreted in terms of structure **24-A** as the favored rotational isomer in agreement with the extended Octant rule for β,γ-unsaturated carbonyl compounds.[8,11,12] In addition, the isomer 24-A would be responsible for the positive CD band centered at 222 nm. Whereas (2*S*)- compounds show a positive Cotton effect around 220 nm, (2*R*)-series of compounds exhibit a negative Cotton effect near 220 nm as shown in the structures 36 and 3 7. Thus, given the sign of the n ⟶ π* Cotton effect one can determine the absolute configuration at the a-position in the a-alkyl-Q-a,P-unsaturated ester. The presence of oxygentated or aminated group at the S-position does not exert any influence on the sign of n ⟶ π* Cotton effect.

In summary, the absolute configuration at the alkylated carbon center can be determined by CD with confidence. We have unequivocally shown that for these examples, the 2S-compounds have a positive Cotton

effect, and the 2R -compounds have a negative Cotton effect. This may be a general phenomenon for α-alkyl (*E*)-β,γ-enoates.

We thank Dr. K. Kuriyama of Shionigi Research Laboratory for the CD spectral measurements of some β,γ-unsaturated esters and helpful discussions. We also thank Prof. T. Shingu, Kobe Gakuin University, for recording ^{1}H-NMR spectra (400 MHz).

Experimental Section

Spectra. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in solvents, as indicated in the Tables I and II. Circular dichroism were measured with a JASCO J-500A spectrometer in solvents, as indicated in Tables I and II at 25 ~ 30 ᵒC. The ^{1}H-NMR spectra were recorded on a Bruker AM-400 spectrometer in deuteriochroroform. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane.

Materials. All homochiral materials have been fully chracterized spectrally and have elemental compositions determined by high-resolution mass spectroscopy and/or combustion analysis. All optically active materials have been presented in references la, 1d, and 2.

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